

Effect of Double Dose of Aqueous Procaine Penicillin to Treat Gonorrhea in Men

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AN earlier study at the Alameda County Health Department venereal disease clinic, Oakland, Calif., indicated that gonorrhea can still be treated effectively by a single intramuscular injection of a sufficiently large dose of rapidly acting penicillin (1). In the men observed in that study, the single intramuscular injection of 2.4 million units of aqueous procaine penicillin G (APP) recommended by the Food and Drug Administration and the Public Health Service (2) and subsequently adopted by the joint U.S. military forces (3) was not always sufficient to eliminate *Neisseria gonorrhoeae*, presumably because some strains were relatively penicillin resistant. For women, however, doubling the dose to 4.8 million units injected intramuscularly at one session cured the entire group, and it was hypothesized that the cure rate might be similarly raised in men if the dose were doubled.

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The present study tested this hypothesis in 830 men treated alternatively with either the 2.4- or 4.8-million-unit APP regimen from March 12, 1969, to October 7, 1969. (The Alameda County Health Department venereal disease clinic is located in Oakland, Calif., a port of debarkation from Vietnam. Gonorrhea acquired by U.S. servicemen in the Far East, particularly in Vietnam, has been reported often as resistant to treatment (4-6). Presumably, therefore, many resistant strains of *N. gonorrhoeae* should have been encountered in this series).

Method and Materials

Gonorrhea was diagnosed by the presence of a purulent urethral discharge after sexual exposure. The diagnosis was confirmed in all instances by demonstrating *N. gonorrhoeae* in a gram-stained smear of the urethral exudate. The smears were corroborated by isolating the organism through the use of a Thayer-Martin culture (7) and were subsequently substantiated biochemically.

Patients were assigned randomly to two treatment groups. Group C received 2.4 million units of APP, and group X received double this dose, 4.8 million units. The injections were made into one or both

buttocks, using one or two single-dose, prefilled, disposable syringes, each containing 2.4 million units of aqueous procaine penicillin G (A). All doses were administered intramuscularly in one session.

The age range of patients in group C was 15–60 years, and in group X it was 16–54 years. The mean age of either group was 25 years. There were no statistically significant differences in the age distribution of the two groups ($P > 0.5$, chi-square test).

At the followup evaluation, specimens for culture were obtained from the urethral meatus. Patients who failed to return for reexamination at the specified time (between the second and fourth days after treatment) were deleted from the study. The earlier work (1) presented the rationale for the 4-day limit via a chart depicting the chronology of treatment, remission, and reinfection.

Treatment was considered a failure if, when the patient was reexamined, there was laboratory evidence of persisting *N. gonorrhoeae*. These patients were retreated with either APP or a broad-spectrum antibiotic.

Results

A total of 437 patients entered group C, but only 194 could be evaluated for the effect of APP (44.4 percent). Similarly, 393 patients entered group X, but only 140 completed the study (35.6 percent). The variation of 44 patients entering the study between groups C and X was attributed to penicillin hypersensitivity and, therefore, these 44 patients were deleted from the study.

Table 1. Results of therapy with aqueous procaine penicillin G given intramuscularly to men with gonococcal urethritis, Oakland, Calif., March 12–October 7, 1969

Variant	Total	Group C ¹ Group X ²	
		Number	
Completed study ³ -----	334	194	140
Cured-----	315	178	137
Treatment failures---	19	16	3
Side effects-----	2	0	2
	Percent		
Completed study ³ -----	40.2	44.4	35.6
Cured-----	94.3	91.8	97.9
Treatment failures---	5.7	8.2	2.1

¹ 2.4 million units at 1 session.

² 4.8 million units at 1 session.

³ Patients who did not keep appointments for reexamination were lost to followup.

Table 2. Results of treatment of men for gonococcal urethritis, by age, Oakland, Calif., March 12–October 7, 1969

Age (years)	Entered study	Completed study		Cured		Side effects
		Number	Percent	Number	Percent	
Under 20--	132	42	31.8	42	100.0	-----
20-29-----	563	210	37.3	198	94.3	1
30-39-----	93	53	57.0	47	88.7	-----
40-49-----	32	22	68.8	22	100.0	1
50-59-----	9	6	66.7	5	83.3	-----
60-69-----	1	1	100.0	1	100.0	-----

Of the 496 patients who were dropped, 494 failed either to return for followup evaluation, or returned beyond the fourth day after treatment. The other two, both of whom were in the higher dose group X, did report back, but had to be dropped because the urethral smears, when cultured, were overgrown with contaminating microflora, preventing positive identification of *N. gonorrhoeae*.

The 2.4-million-unit dose of APP was curative in 92 percent, in agreement with the response obtained in the earlier work (1). However, the 4.8-million-unit dose was almost completely effective, eliminating the organism in 98 percent of those who completed the study (table 1). The difference in cure rates between the two groups was statistically significant to indicate a substantial therapeutic advantage for the double dose ($P < 0.02$, chi-square test).

There was some tendency for treatment to be more effective in younger men (table 2). However, significantly fewer of the men up to 29 years old as compared with the men over 29 completed the study. Separate analysis of the two treatment groups disclosed no significant differences among the age classes of those cured in group X. In group C, only the 30–39-year-old class differed significantly from the others, there being fewer cures in this class than in all the others ($P < 0.01$, chi-square test).

Adverse reactions occurred in only two patients, both of whom were in the higher dose group X. Both reactions were immediate. One patient, 40 years of age, reported lightheadedness, a bitter taste in his mouth, and a dry mouth. He did not lose consciousness, and the clinician diagnosed the state as "possible vasovagal syncope." The other patient, 27 years of age, had a more severe reaction. Immediately after the injection he convulsed, lost consciousness

ness, and exhibited tonic-clonic contractions, with clenched teeth, combativeness, and opisthotonus. (There was no interference with his respiration.) He responded to emergency treatment (100 mg. of diphenhydramine hydrochloride given intramuscularly and oxygen), regained consciousness in about 3 minutes, but remained anxious, confused, and amnesic. He was admitted to the hospital for 24-hours' observation. The clinician's impression was that a grand mal seizure rather than true anaphylaxis had occurred. (Both of these reactions appear compatible with acute procaine reactions as previously reported in gonorrhea patients who received large doses of APP) (8).

Discussion

The results clearly indicate that penicillin therapy for gonorrhea in men is still effective. Thus, the dosage recommended by the Public Health Service and the Food and Drug Administration, 2.4 million units of APP, is still adequate in most but needs to be increased in a few men. The same applies to the 2.4-million-unit dose which continues to be recommended by the Alameda County Health Department and most other health jurisdictions in California. For the few men who do not respond, data in this paper show that 4.8 million units are nearly always curative. In the rare instance of greater penicillin resistance, as well as in the patient who has a history of hypersensitivity to penicillin, a broad-spectrum agent should be substituted (5, 9).

Why, in studies of gonorrhea, do most male patients (in this study 60 percent) fail to return for evaluation? And why, in the present series, did 9 percent fewer of group X, who were given the larger dose, than of group C, fail to return? The only reasonable explanation seems to be that, in men, gonorrhea is poorly tolerated only when it is producing symptoms. Once rid of the symptoms, men tend to regard themselves as cured and see no reason for continuing treatment or reporting back to the clinic. In this assumption, of course, many are mistaken as clinicians might also be were they to assume (as is sometimes done) that those who did not return were bacteriologically cured. Gonococci can survive while producing mild, nondistressing symptoms or none at all (10). Moreover, some patients who are not cured may look elsewhere for further treatment.

Penicillin is not as effective as it once was against the gonococcus, but at increased dosage it remains

the drug of choice despite the gradual development of bacterial resistance.

At present, the 4.8-million-unit intramuscular dose of APP appears adequate for about 98 percent of the patients. This cure rate is undeniably encouraging. It is an improvement over the rates reported for ampicillin (11) and broad-spectrum agents such as cephaloridine (12, 13), kanamycin (13, 14), and doxycycline (15). Nevertheless, the pattern of microbial resistance is constantly changing (16), and the search for penicillin substitutes must not be relaxed (17).

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SUPPLY REFERENCE

- (A) Wycillin®, Wyeth Laboratories, Radnor, Pa. 19087.

NELSON, MORTON (Alameda County Health Department, Oakland, Calif.): *Effect of double dose of aqueous procaine penicillin to treat gonorrhea in men. HSMHA Health Reports, Vol. 86, March 1971, pp. 285-288.*

Results of massive doses—4.8 million units—of aqueous procaine penicillin G (APP) were compared with the results of 2.4-million-unit doses of the same preparation in the treatment of 334 men with gonorrhea. The lesser dosage, recommended by the Food and Drug Administration and the Public Health Service, has been adopted by U.S. military services.

The study was conducted at the

Alameda County Health Department venereal disease clinic in Oakland during 1969. Oakland is a port of debarkation from Vietnam, a source of penicillin-resistant *Neisseria gonorrhoeae*.

The patients ranged in age from under 20 to 69 years. Treatment usually was more effective in the younger men.

The cure rates, as determined by culture, were 92 percent for the 194 patients who received the

lesser dosage and 98 percent for the 140 patients who received the 4.8 million units. Adverse reactions were reported in two patients who received the larger dose.

The difference in the rates of cure was statistically significant at the $P < 0.02$ level by chi-square test. The results indicated that gonorrhea can still be treated effectively by an intramuscular injection of a sufficiently large dose of fast-acting penicillin.